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**Sustained release compositions for treating periodontal disease.**

This invention relates to compositions/devices and methods for treating diseases of the oral cavity in humans and lower animals using polypropenoic acid compositions/devices for releasing drugs in the oral cavity.

**EP 0 429 225 A1**

# SUSTAINED RELEASE COMPOSITIONS FOR TREATING PERIODONTAL DISEASE NALINKANT CHUNILAL DAMANI

## TECHNICAL FIELD

This invention relates to compositions/devices for treating diseases of the oral cavity, which compositions/devices are placed in or around the periodontal pocket. The invention also relates to methods of using the compositions/devices in humans and lower animals suffering from such diseases.

Periodontal disease, for example, is a major cause of tooth loss in adults. Tooth loss from periodontal disease is a significant problem beginning at age 35, but even by age 15 it is estimated that about 4 out of 5 persons already have gingivitis and 4 out of 10 have periodontitis.

While good oral hygiene, as achieved by brushing the teeth with a cleansing dentifrice, may help reduce the incidence of periodontal disease, it does not necessarily prevent or eliminate its occurrence. This is because microorganisms contribute to both the initiation and progress of periodontal disease. Thus, in order to prevent or treat periodontal disease, these microorganisms must be suppressed by some means other than simple mechanical scrubbing. Towards this end, there has been a great deal of research aimed at developing therapeutic dentifrices, mouthwashes, and methods of treating periodontal disease which are effective in suppressing these microorganisms.

Recent developments in the art are directed toward delivering the therapeutic agent directly to the periodontal pocket, in some cases in a controlled release formulation. Gordon et al. have described the use of a drug-filled polymer hollow fiber. (J.M. Goodson et al., "Periodontal Therapy by Local Delivery of Tetracycline", J. Clin. Periodontol. 6, 83 (1979), J. Lindhe et al., "Local Tetracycline Delivery Using Hollow Fiber Devices in Periodontal Therapy", J. Clin. Periodontol. 6, 141 (1979) and R.L. Dunn et al., "Monolithic Fibers for Controlled Delivery of Tetracycline", in Proc. Ninth Int. Symposium on Controlled Release of Bioactive Materials, Ft. Lauderdale, FL, July (1982). This device is tied around a tooth and gently pressed below the margin of the gingiva so that it resides in the periodontal pocket, and is capable of delivering an effective dose of 2.5 micrograms of tetracycline per day per periodontal pocket for a prolonged period of a week or more. Similar results have been obtained by Coventry and Newman (J. Coventry and H. N. Newman, "Experimental Use of a Slow Release Device Employing Chlorhexidine Gluconate in Areas of Acute Periodontal Inflammation", J. Clin. Periodontol. 9, 129 (1982) and Addy et al. (M. Addy et al., "The Development and in vitro Evaluation of Acrylic Strips and Dialysis Tubing for Local Drug Delivery", J. Periodontol. 53, 693 (1982) using acrylic strips 1mm or more long, impregnated with chlorhexidine, tetracycline or metronidazole, which were inserted into the periodontal pocket with tweezers. Such a strip, formed from ethylcellulose impregnated with metronidazole, is disclosed by Loesche in U.S. Patent No. 4,568,538 (February 1986). Another strip, employing a water soluble polymer of a particular elasticity and viscosity, is disclosed by Suzuki et al. in U.S. Patent No. 4,569,837.

In addition to the above approaches, the prior art also discloses using putty-like compositions containing an antimicrobial for insertion into the periodontal pocket. See U.S. Patent 4,650,665, March 17, 1987 to Kronenthal et al., incorporated herein by reference.

The present inventor has discovered that using polypropenoic acid as the material forming the composition/device allows for efficient/good devices to be formed.

Previous attempts to effectively treat periodontal pockets have not been desirably successful. This is largely due to the fact that a periodontal pocket cavity is very narrow and convoluted or tortuous, making it nearly impossible to fill the entire cavity with a treatment product.

This invention, utilizing highly swell able polymer eliminates such problems. Once a product of this invention is placed in periodontal cavity, the polymer swells, expands, and reaches narrow crevices and furcations of the treated cavity, carrying active agent throughout the cavity. This provides most desirable efficacy at treatment site.

It is therefore an object of the present invention to provide polypropenoic compositions/devices suitable for treating periodontal disease and other diseases of the oral cavity.

It is a further object of the present invention to provide such compositions/devices using mixtures of polypropenoic acid and other polymers.

It is still a further object of the present invention to provide a method of treating periodontal disease.

All percentages and ratios used in here are by weight unless otherwise indicated.

All measurements are made at 25° C unless otherwise indicated.

SUMMARY OF INVENTION

The present invention relates to compositions/devices and methods for treating diseases of the oral cavity by inserting the compositions/devices around or into the periodontal pocket of humans and lower animals. The compositions/devices comprise polypropenoic acid and an agent providing relief of diseases of the oral cavity such as periodontal disease.

DETAILED DESCRIPTION OF THE INVENTION

The essential as well as optional components of the compositions/devices of this invention are described below.

15 Polymer

The polymer used in the present compositions is referred as super absorbent polymer and is defined as polypropenoic acid. The material is a polyacrylic acid which is lightly crosslinked with an agent such as divinyl glycol, trimethylpropane triacrylate and polyallyl sucrose. These materials are provided as Dry Tech 512 by Dow Chemical Company, Aqualac-CA by Nippon Shokubai and NALCO-1181 by Nalco Chemicals. Other materials related to the above include Polycarbophil by B. F. Goodrich Company.

A preferred material is Dry Tech-512 which is polyacrylic acid crosslinked with 0.004 mole percent of trimethylpropane triacrylate. The carboxylic groups can be neutralized with, for example, a sodium base to an extent of 75% or more.

A most preferred polymer useful in the present invention has very high, nearly infinite molecular weight in its crosslinked form which is estimated to be 2 million to 10 million or even higher. Unit segments of crosslinked polymer have a range of number average molecular weight from about 50,000 to about 1 million. The polymer is used in the present compositions at a level of from about 1% to about 99%, preferably from about 10% to about 75%, most preferably from about 20% to about 50%.

30 Drug Active

The drugs useful for use in the present compositions/devices are varied and many and include any agent which provides treatment of the disease. Some therapeutic agents which are amenable to delivery by this means and are potentially of value for periodontal therapy, include (but are not limited to) antimicrobial/antibacterial agents such as iodine, sulfonamides, mercurials, bisbiguanides, or phenolics; antibiotics such as tetracycline, neomycin, kanamycin, metronidazole, or clindamycin; antiinflammatory agents such as aspirin, naproxen, ibuprofen, flurbiprofen, indomethacin, eugenol, or hydrocortisone; immune-suppressive or stimulatory agents such as methotrexate or levamisole; dentinal desensitizing agents such as strontium chloride or sodium fluoride; odor masking agents such as peppermint oil or chlorophyll; immune reagents such as immunoglobulin or antigens; local anesthetic agents such as lidocaine or benzocaine; nutritional agents such as amino acids, essential fats, and vitamin C; antioxidants such as alphanatocopherol and butylated hydroxy toluene; lipopolysaccharide complexing agents such as polymyxin; or peroxides such as urea peroxide. It is recognized that in certain forms of therapy, combinations of these agents in the same delivery system may be useful in order to obtain an optimal effect. Thus, for example, an antibacterial and an antiinflammatory agent may be combined in a single delivery system to provide combined effectiveness.

The drug active is used at a level of from about 1% to about 99%, preferably from about 5% to about 75%, most preferably from about 10% to about 50% of the compositions/devices. The compositions/devices, for example, are designed to release drug at a rate to provide concentration of from about 10 $\mu$ g to about 2000 $\mu$ g, preferably from about 50 $\mu$ g to about 1000 $\mu$ g, most preferably from about 100 $\mu$ g to about 500 $\mu$ g per milliliter of the gingival crevicular fluid of a treated periodontal pocket. Desired release rates can be achieved by altering ratios of components in a composition.

55 Optional Components

In addition to the drug active, the compositions/devices of the present invention may include a variety of optional components. Such components include, but are not limited to, surfactants, other polymers,

viscosity controlling agents, complexing agents, antioxidants, gums such as guar gum, waxes/oils such as castor wax, castor oil, glycerol, dibutyl phthalate and ethyl sebacate as well as many others.

The additional polymer may include a number of polymers such as methyl cellulose, polycaprolactone and polylactide. A particularly preferred polymer is a copolymer of lactide and glycolide. Lactide monomeric species preferably comprise 15% to about 85%, most preferably from about 35% to about 65%, of the polymers while glycolide monomers comprise from about 15% to about 85% of the polymer, preferably from about 35% to about 65% on a molar basis. The molecular weight lies in the range of from about 1000 to about 120,000 (number average). These polymers are described in detail in U.S. Patent 4,443,430, April 17, 1984, to Mattei incorporated herein by reference.

If used, these optional components comprise from about 0.1% to about 50%, preferably from about 0.5% to about 25% of the total composition/device.

#### METHOD OF MANUFACTURE

Method of manufacturing the compositions/devices of this invention are disclosed in the Examples.

The following Examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The Examples are given solely for the purpose of illustration and are not to be constructed as limitations of the present invention as many variations thereof are possible without departing from its spirit and scope.

#### EXAMPLE I

The following is an exemplary composition/device of the present invention.

	<u>Weight %</u>
Tetracycline hydrochloride	50
Polypropenoic acid	22.7
Poly(lactyl-co-glycolide)/50:50 copolymer	22.7
Propylene Carbonate	4.6

The above composition can be prepared in a number of different ways. One way is as follows: Polymer is charged into 110°C, electrically heated mixer, equipped with high shear Sigma type rotor blades. Propylene carbonate is added and mixed into the polymer. The drug is added and mixed until uniform. The drug polymer blend is removed for further processing into desired size and shaped devices.

The compositions/devices of the invention of this application are inserted into or around the periodontal pocket or gingival region, and are administered in the form of a particle, film or sheet. The size, shape, and thickness can be changed according to the condition of the periodontal disease to be treated and they are not particularly critical. Ordinarily, the size, shape, and thickness are changed according to the size of the periodontal pocket of the patient or the condition of the gingiva. The devices may be for example of a size such that the thickness is in the range of 0.01 to 2mm, preferably from about 0.1 to about 1mm; the width in the range of 0.1 to about 5mm, preferably from about 0.2 to about 4mm; and the length in the range of from about 1 to about 15mm, preferably from about 3 to about 10mm.

#### EXAMPLE II

Given below is another composition/device of the present invention:

Chlorhexidine acetate	40
Polypropenoic acid	35
Methyl Cellulose	20
Glycerol monostearate	5

EXAMPLE III

Given below is still another composition/device representative of the present invention:

	Wt. %
Metronidazole	40
Polypropenoic acid	30
Polycaprolactone	25
Pluronic F-68	5

EXAMPLE IV

Given below is still another composition representative of the present invention:

	Wt. %
Flurbiprofen	20
Polypropenoic acid	25
Xanthan Gum	20
Poly lactide polymer	25
Polyethylene glycol	10

**Claims**

1. A composition suitable for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity comprising polypropenoic acid and a drug active.
2. A composition according to Claim 1 wherein the number average molecular weight of individual polypropenoic acid units is from about 50,000 to 1 million, which are crosslinked to provide nearly infinite molecular weight.
3. A composition according to Claim 1 or 2 wherein the drug active is selected from the group consisting of antiinflammatory agents, antibiotics, peroxides, anesthetic agents and vitamins.
4. A composition according to any of Claims 1-3 wherein the concentration of drug active is from about 5% to about 75%.
5. A composition according to any of Claims 1-4 wherein the concentration of the drug active is from about 10% to about 50% and the active is selected from the tetracycline group of antibiotics.
6. A composition according to any of Claims 1-5 which in addition contains another polymer.
7. A composition according to any of Claims 1-6 wherein said additional polymer is a copolymer of glycolide and lactide.
8. Use of polypropenoic acid in the manufacture of a composition suitable for insertion into or around the periodontal pocket of a person or lower animal suffering from diseases of the oral cavity wherein a drug active is included with monoolein in the composition.
9. Use of polypropenoic acid according to Claim 8 wherein the monoolein concentration is from about 1% to about 90%.
10. Use of polypropenoic acid according to Claim 8 or 9 wherein the drug active is selected from the group

consisting of antiinflammatory agents, antibiotics, antimicrobials, peroxides, anesthetic agents, vitamins and mixtures thereof.

11. Use of monoolein according to Claim 10 wherein the drug active is selected from the tetracycline group of antibiotics.

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# EUROPEAN SEARCH REPORT

Application Number

EP 90 31 2250

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)
P,X	DERWENT FILE SUPPLIER WPIL, 1990, accession 90-053523 [08], Derwent Publications Ltd, London, GB; & JP-A-2 004 710 (NIPPON SODA) * Abstract *	1	A 61 K 9/70 A 61 K 9/22 A 61 K 47/14
X	US-A-4 250 163 (T. NAGAI) * Abstract; column 1, lines 15-27; column 5, lines 22-26; column 5, line 62 - column 6, line 16; column 7, lines 47-56; tables 1-3; examples 3,9,10; claims *	1-6	
X	EP-A-0 275 550 (TEIKOKU SEIYAKU) * Abstract; page 2, lines 5-12; page 3, lines 21-41; page 4, lines 15-54; examples (in particular page 9, example 4); claims 1-3,10,17,19 *	1-6	
Y	EP-A-0 130 690 (TEIJIN LTD) * Abstract; page 3, lines 5-28; page 5, line 30 - page 6, line 6; page 6, line 21 - page 8, line 12; example 5 *	1-6	TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Y	WO-A-8 502 092 (BIO-MIMETICS INC.) * Abstract; page 7, line 22 - page 8, line 7; page 19, lines 1-35; page 21, lines 16-19 *	1-6	A 61 K
A	EP-A-0 241 178 (ROHTO PHARMACEUTICAL CO.) * Abstract; claims *	1-6	
D,A	US-A-4 568 536 (R.L. KRONENTHAL) * Column 2, lines 10-39; column 6, line 21 - column 7, line 11 *	7	
		-/-	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 07-02-1991	Examiner HOFF P.J.L.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

EPV FORM 1503 03.82 (P0401)



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 267 617 (THERATECH, INC.) * Abstract; page 3, lines 34-42,51-55; example VII; claims * ---	8-11	
A	"The Merck Index", 10th edition, 1983, pages 19-20, Merck & Co., Inc., Rahway, N.J., US * Abstract no. 126: "Acrylic acid" * -----	1	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
Place of search THE HAGUE		Date of completion of the search 07-02-1991	Examiner HOFF P.J.L.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			